REVIEW ARTICLE

Prognostic impact using intensive intraoperative complementary technologies in cerebral gliomas. Literature review and presentation of 1 case.

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ABSTRACT

Introduction: *The management of cerebral gliomas during the last four decades has undergone relevant changes in terms of its study and treatment. Among these changes is the development of imaging, neurophysiological and histopathological techniques. The present study attempts to estimate the impact that the use of these technologies has had on the prognosis of patients.* ***Material and Method:*** *Comprehensive review of the literature in digital and print media covering mostly publications and communications from the 1980s to the present. 1 case recently submitted to surgery by the authors in which several of these tools were used is exposed, presenting the analysis that was carried out in the surgical planning.* ***Results:*** *The literature shows consistent but discrete improvements in the prognosis associated with the use of intraoperative complementary technologies in cerebral gliomas, related to the help they would provide in the extension of tumor resection and functional preservation.* ***Conclusions:*** *The intensive use of the complementary technologies described seems advisable if surgical planning anticipates well-founded benefits in terms of morbidity and mortality for a particular patient. Caution should be exercised in anticipating and generalizing the global prognostic impact they may have, a benefit that is consistent in the literature but currently seems modest in general terms especially for high grade gliomas.*

Key words: *glioma, neuronavigation, neuromonitoring, vigil craniotomy, functional magnetic resonance.*

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INTRODUCTION

Among primary intraparenchymal brain tumors, gliomas represent the most common type despite having a relatively low incidence (3-5/100,000 for high-grade gliomas)[1,2,3]. Based on their histopathology, gliomas have traditionally been categorized into 2 large groups: low- and high-grade gliomas, this derived from the most widely accepted and used histopathological classification that classifies them into 4 degrees and that relates pathological and histological findings with clinical behavior and prognosis: histological grade gliomas 1 and 2 are considered low-grade, leaving those of grades 3 and 4 qualified as high grade, being in general better the prognosis to lower the degree (WHO, see classification reference). There are subclassifications of these tumors in relation to their original cells where the predominant subtypes are astrocytomas, oligodendrogliomas and ependymomas. Within these subgroups there are variants related to different aspects related to histopathology, immunological markers and chromosomal and genetic characteristics. Although the prognosis of high-grade gliomas generally has an extremely ominous clinical behavior and prognosis, they present a great internal variability as a diagnostic type, which has motivated the inclusion of patients in subgroups in an attempt to have more adjusted prognostic approaches.[4,5]

Since the 1980s, the inclusion and development of a series of tools linked to technological developments of great sophistication can be recognized, from the diagnostic stage to the therapeutic stage for the general management of cerebral gliomas. The refinement of diagnostic imaging techniques (magnetic resonance, spectrography, functional magnetic resonance, tractography, magnetoencephalography, among others), the advancement of surgical techniques and their technological, anesthetic and electrophysiological assistance (microsurgical and stereotaxy advances, neuronavigation, ultrasound guidance, vigil craniotomies, intraoperative multimodal neuromonitoring, cofocal and fluorescence microscopy, intra-histopathology pavilion and in vivo among others) as well as the enormous progress in radiotherapy, chemotherapy and other systemic treatments, together with general and palliative support, allow us to have today a diagnostic and therapeutic arsenal much higher than what we had available only 40 years ago.[4,6-9]

However, we can affirm without fear of being mistaken that the evidence is categorical in showing us a disrelation between what we could intuitively expect with all these advances and the real impact that they ultimately prove to have on the prognosis of the generality of patients: despite the application of all strategies aligned with the state of the art, the prognosis for high-grade gliomas remains poor, with an average survival of around 14 months, representing an average improvement in the 2-month vital prognosis after 4 decades of innovation and technical progress[1-3,10-14]. For low-grade gliomas the situation is different in relation to their prognosis, however controversy persists in several aspects of their management, from the real impact that the degree of resection has on the overall prognosis by associating surgery with radio and chemotherapy, to the aggressiveness and surgical limits recommended for their resection in eloquent areas.[10,12,13,15]

MATERIAL AND METHOD

A review of the relevant literature and 1 clinical case recently treated by the authors are presented, which is related and serves as the axis for the review and conclusions.

For the literature review, an exhaustive search was used through digital platforms (Medline, Embase, Cochrane Database of Systematic Reviews, MedlinePlus, Ovid, Science Direct, Google Scholar) of the keywords associated with the topics of this article. For publications prior to the year 2000, direct bibliographic sources were mostly used according to the references of review articles, academic communications, congresses and book chapters.

As for our clinical case, there is a 30-year-old male patient with no morbid history of any kind, who four months before the imaging diagnosis presented multiple self-limiting episodes of language alterations, characterized by his relatives as anomie and loss of fluency, as well as periods of confusion of about 10 minutes of duration repeated on about 5 occasions only for 1 day according to the anamnesis directed and repeated by several medical examiners.

Without new findings in history, 2 weeks before diagnosis, mainly motivated by high cervicalgia, a study was carried out with scanner and magnetic resonance imaging that revealed the presence of 2 brain lesions, one parieto-temporal and another parietal left, concordant with low-grade gliomas, being striking the observation of clearly independent lesions in spatial terms despite their anatomical proximity **(Figures 1 and 2).**

This condition of multiple lesions without recognizable anatomical contact was observed in 3 different MRIs to which the patient underwent the week before surgery, performed in different radiological centers and reported by different neuroradiologists.

The initial clinical evaluation of the patient did not reveal any neurological deficits. In particular, oral and written language did not present alterations of comprehension or expression, nor were dyscalculia or dyspraxias detected. Given the clinic and the location of the lesions, functional magnetic resonance imaging was performed for evaluation of the language and motor area, and tractography for location of the cortico-spinal bundle. These studies showed an intimate anatomical relationship between the area of comprehensive language and the motor area of the right hand with the lower and anterior aspects of the larger tumor, while the cortico-spinal tract passed about 1 medial centimeter to the more medial aspect of the major tumor **(Figures 3 and 4)**.

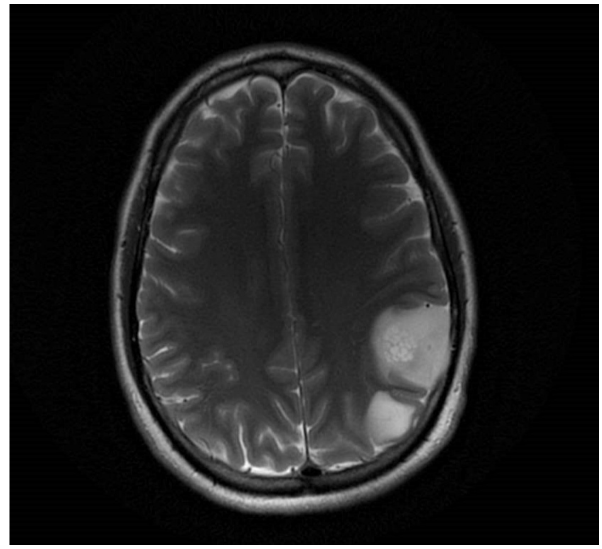


Figure 1. Preoperative Magnetic Resonance Imaging, axial sequence in T2. In all the sequences and projections, 2 close but completely separated lesions were observed.

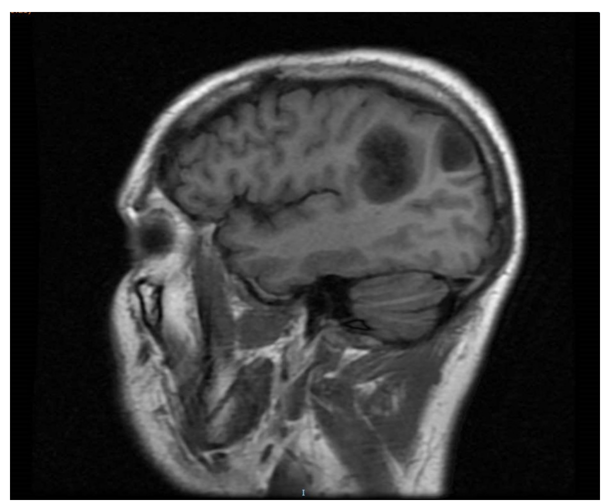


Figure 2. Preoperative MRI, T1 axial sequence. In all the MRIs performed during the preoperative study, 2 separate lesions were observed. In all studies, the radiological interpretation was low-grade gliomas.

Considerations in surgical planning

There is consensus that resection should be sought as completely as possible in low- and high-grade gliomas, whenever possible while respecting eloquent areas. The literature is consistent in showing that macroscopically complete resections in low-grade gliomas leads to statistically higher prognoses than those of subtotal resections, with series indicating survivals of up to 100% at 10 years[1,3,5,6,16], along with a marked reduction in progress to higher histological degrees[10,12,13]. For high-grade gliomas the central goal of surgery is also to achieve a macroscopically complete resection, although naturally the prognostic improvement is in comparison modest[2,3,11,14,17]. With these objectives, the intraoperative technological assistance for this case was evaluated:

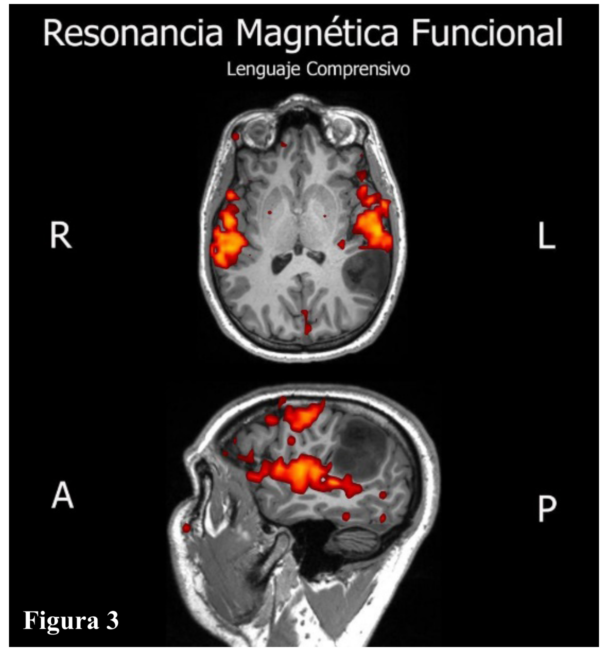
Neuronavigation based on magnetic resonance imaging

For our patient, in the case of two lesions with eloquent areas (language and motor) closely related to them according to functional magnetic resonance imaging and with clinical deficit concordant presentation, neuronavigation was used from surgical planning (Fiagon AG Medical Technologies, Germany)

The use of frameless neuronavigation, especially for lesions in functionally significant areas, in low-grade gliomas and in deep locations, has become a standard.[1,3,13]

In lesions that compromise the cortex, navigation allows greater precision in the guiding stage for craniotomy. After this there will be increasing distortion as tumor dissection and resection progress due to changes in the position of brain structures versus pre-operative imaging (drainage of spinal cephalal fluid, manipulation and tumor resection). For this reason, having computed tomography equipment and ideally with magnetic resonance within the pavilion associated with navigation offers advantages in the real-time delineation of surgical objectives[1,2,5-7]. Stereotactic navigation associated with high-field resonance also allows anatomical-functional guidance in glioma surgery. A number of other navigation-associated innovations have been proposed and are being implemented, including the use of metabolic/structural markers, 3D visualization, and axonal beam tracking.[1,8]

In our case, the navigation was based on the last preoperative resonance performed on the



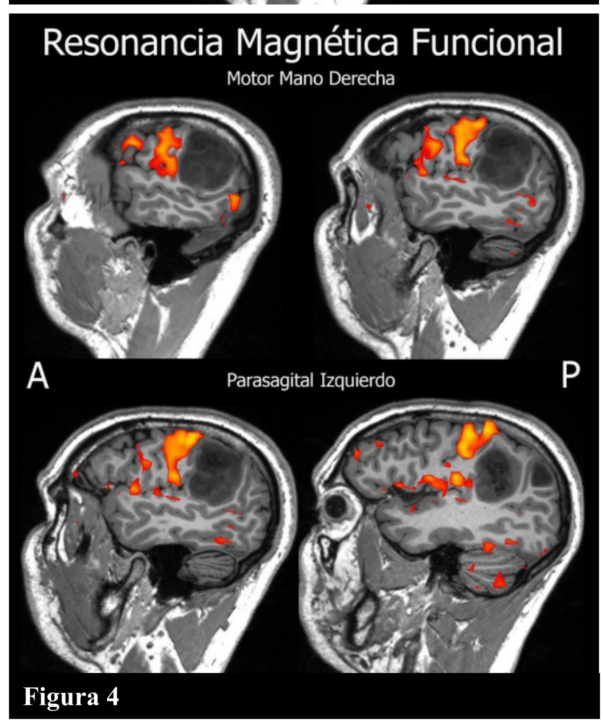


Figure 3 and 4. Functional magnetic resonance imaging: the motor study of the right hand and comprehensive language show the close relationship of the activated areas with the largest lesion (anterior).

patient. Although the location of the incision and craniotomy initially defined by the surgeon based on topographic anatomy and the referents of conventional preoperative images coincided with the location indicated by the navigation team, the use of this technology proved useful to corroborate the cortical limits of both lesions and guide the depth of the projected resection taking care of the path of the left spinal cord bundle.

Vigil craniotomy

Taking into account the relationship of the larger lesion with language area both by the presentation clinic and by functional magnetic resonance imaging, it was considered essential to perform functional language tests under neuromonitoring and multimodal stimulation using a "sleep-vigil-sleep" anesthesia protocol.

During the surveillance phase and performing a bipolar stimulation, the cerebral cortex exposed in detail was mapped with stimuli up to 8 milliamperes (Nim Eclipse, Medtronic USA, 32 channels) Together with the stimulation, during the wakefulness phase extensive tests of oral language emission, auditory and visual comprehension, semantic memory and calculation were performed. Only with the final stimulation of 8 milliamperes in the lower area of the craniotomy was a drop in language fluency obtained during the inversion of numerical series, which coincided with the lower limit of the most superficial aspect of the tumor and with what was indicated by the preoperative functional magnetic resonance imaging. After the language tests, the patient was again deepened in general anesthesia and re-intubated.

As the resection of the larger lesion deepened, monopolar subcortical motor stimulation tests were performed to preserve the spinal cortex tract unscathed. Despite the expected brain shift resulting from progressive tumor resection, navigation was very closely oriented in terms of the safe depth that could be reached as found in the post-operative images **(Figure 5).**

Motor stimulation did not trigger responses at any point in the tumor bed until resection was complete. The monitoring of somato-sensory and motor evoked potentials showed no modifications with respect to the baseline once the surgery was completed.

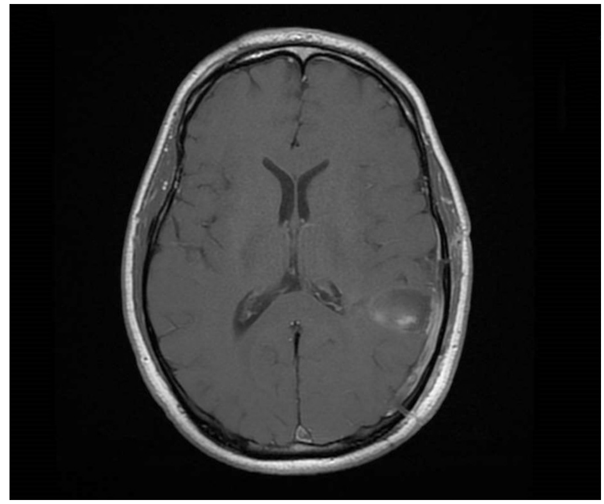


Figure 5. Postoperative control magnetic resonance imaging (3 months), axial T1 contrasted: no tumor remnants or appearance of new lesions are observed.

At this point it seems important to consider that functional resonance is not an entirely reliable predictor for the location of language areas. Different studies show sensitivities ranging from 59 to 100%, with specificities between 0 and 97%[1-5,11]. Regarding motor function, studies with better methodology and a greater number of patients indicate a specificity and sensitivity of around 80%, so in general it can be concluded that functional resonance is a guideline that can in no way replace monitoring, direct stimulation and clinical/electrical mapping during surgeries when necessary[1,3,4]. Functional mapping has been shown to improve accuracy in high- and low-grade glioma surgeries, thus allowing for greater resections while preserving eloquent areas. [10-13]

Ultrasound-guided localization and resection

Intraoperative echotomography is a universally available resource in highly complex health centers that has been used and validated for decades[19,20,25]. Navigation by sonography allows to identify and differentiate solid tumor regions, cystic, edema and gliosis, being especially useful in heterogeneous lesions and with necrotic, cystic or hemorrhagic components, also allowing to define the most appropriate surgical corridors. Reports of up to 95% complete resections are found in high-grade gliomas.[3,10,19,20]

Ultrasound, especially intraoperative ultrasound, is strongly operator dependent and requires a significant learning curve especially for deep lesions. Given the relative structural homogeneity and absence of relevant edema in low-grade gliomas, ultrasonography does not seem as useful as in the case of high-grade gliomas, and in general the consensus is that the delimitation of this type of lesions is more precise with navigations based on magnetic resonance imaging.[1,3,13,19,20,21]

Intraoperative histological sampling

In expert hands and eyes, intraoperative biopsies offer the highest degree of safety in terms of the location of the tumor lesion[2,3]. For high-grade lesions, the use of spectrometry and other molecular techniques can help to pinpoint the tumor grade and its spatial limits.[4,5,22,23,24]

Augmented visualization methods under the surgical microscope

White light binocular microscopy can be considered a standard in the management of intraparenchymal brain tumors for decades. The most recent introduction of augmented microscopic visualization methods has contributed to better confirmation and delimitation of lesions. Among these techniques are the use of 5-aminolevulinic acid under blue light, cofocal microscopy to obtain histological images in vivo, microspectrofluorometry, differentiation of wavelengths of normal versus tumor tissue based on their metabolisms in real time, use of nanoparticles, among many techniques and strategies in development, all of which can be useful especially in the delimitation of high-grade tumors.[24,25]

RESULTS

The literature shows that all the complementary technological methods described represent a contribution to tumor identification and delimitation: image-based navigation allows us to plan biopsies, surgical corridors and achieve broader resections; intraoperative sampling allows us to confirm the tumor diagnosis and get closer to its origin and grade; electrophysiological monitoring helps to identify and respect eloquent areas while helping to expand safe resections; Microscopy techniques with augmented visualization help identify tumor remnants and areas of infiltration into more aggressive tumors.

Based on the best available evidence and the specific situation, for the clinical case presented, a macroscopically complete resection of the two lesions was achieved with the use of neuronavigation (based on preoperative magnetic resonance imaging) together with electrophysiological and clinical monitoring during a vigil craniotomy **(Figure 5)**.

The normal-looking gyrus visible in the preoperative resonances, located between the two tumors, was identified with certainty in the intraoperative period under direct vision corroborated by navigation, being resected after demonstrating absence of functional expression and considered as an edge of low thickness between both lesions.

In the postoperative period, the patient presented with dysphasia (anomie), agraphia and alexia that progressively reversed until the absence of language deficit was observed in all its aspects after 3 weeks after surgery, not presenting motor, sensory or praxia alterations at any time of the evolution.

The delayed histopathological and immunohistochemical study indicated for both lesions the diagnosis of high-grade glioma (mutated anaplastic astrocytoma IDH-1, WHO grade III)

DISCUSSION

We know that gliomas are diffuse tumors whose cells are scattered in the brain parenchyma already at the time of diagnosis[1-4.25]. Despite this, the accumulated evidence is consistent in indicating that major macroscopic resections positively impact disease-free survival, the rate of progression and transformation to more aggressive lesions, and total survival for all subtypes of gliomas[1,2,3,15,25] on of broad resections in high-grade gliomas remains modest, however there is no doubt that it represents a real and consistent improvement in the general management of these cases and that it is the best that can be offered to patients today in the stage prior to radio and chemotherapy.

It is very important to carry out a case-by-case analysis, be critical and actively seek a rational use of complementary technologies based mainly on the projected impact of their use for each specific patient. For example, in the case presented, neuronavigation, multimodal neuromonitoring and vigil craniotomy were considered useful. In other cases, the use of ultrasonography, fluorescence or intraoperative sampling could be very useful for the identification and resection of lesions.

We believe that the fundamental concept that emerges from the above is that standards or general rules for the use of these technological aids cannot be assumed, and that it should always be as rigorous as possible in its use taking into account the characteristics of each patient, each tumor, and the projection of the real impact on the functional prognosis and survival. In some cases, none of these technologies has been shown to contribute anything significant to the evolution of patients (for example in recurrences of high-grade tumors and in severely sequelae patients, among others)[1,2,3,25], while some scenarios will merit the intensive use of a large part of them to achieve the greatest amplitude in tumor resection while preserving neurological indemnity.

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